

# Cerebral and cardiac signal monitoring in fetal sheep with hypoxic-ischemic encephalopathy

Citation for published version (APA):

Zwanenburg, A. A. (2015). *Cerebral and cardiac signal monitoring in fetal sheep with hypoxic-ischemic encephalopathy*. [Doctoral Thesis, Maastricht University]. Maastricht University.  
<https://doi.org/10.26481/dis.20151119az>

## Document status and date:

Published: 01/01/2015

## DOI:

[10.26481/dis.20151119az](https://doi.org/10.26481/dis.20151119az)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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## Valorisation



The personal and societal burden of hypoxic-ischemic encephalopathy (HIE) is immense. Infants with HIE will often experience lifelong effects, e.g. motor and learning disabilities, cerebral palsy, and blindness. Neonatal encephalopathy globally leads to 50 million disability-adjusted life-years (DALY). In comparison, the entire spectrum of cancer was estimated to lead to 169 million DALY globally. Reducing incidence and/or severity of HIE decreases the healthcare and personal costs involved in providing lifelong treatment and support.

This thesis advocates the use of computer-assisted analysis to allow physicians to make a more accurate decision on intervention and treatment. The aim is to use computer algorithms to provide timely and non-redundant information about the fetus or infant that is sensitive and specific to the issue being investigated. In this thesis, such information was based on electro-physiological signals. In chapter two, for example, ECG signal characteristics were used as markers for fetal metabolic compromise that would necessitate immediate intervention.

The design of clinical devices for fetal monitoring is in general based on relatively simple principles of preset threshold values. Alarms are generated after breaching thresholds. In general, threshold values for alarm limits are determined empirically, using a relatively small data set for training and algorithm validation. This approach works to some degree, but using small data sets increases the risk of overfitting. Overfitting means that the algorithm is too specifically designed for the data available for training and evaluation. Due to overfitting, an algorithm will perform less well when analysing new and unseen data. For example we discovered in our analysis that the Neoventa STAN S31 device used for ST waveform analysis did not take into account the negative changes in T/QRS ratio. We speculate that the devices' algorithm to assess only positive T/QRS ratio changes was likely because the data reported by the developers of the algorithm did not show negative T/QRS ratio changes as a response to fetal metabolic compromise. Negative T/QRS ratio changes were, however, present within our data set. Consequentially, the device did not perform well in our investigation. The same issue may also be a contributing factor to the lack of improvement in primary outcome by ST waveform analysis that was cited in the meta-analyses referred to in chapter two. Resources went into developing a device that, after expensive clinical trials, did not seem to yield the improvement expected by both the developers and clinicians, and public money was also invested in purchasing said devices for clinical use. Choices made in algorithm design have both healthcare and economic implications. This means that the decision making process that leads to the final algorithm and the data set on which it is tested need to be carefully evaluated to avoid accidental oversights.

One way to make algorithm development and design less prone to overfitting and other biases is to rely on machine learning methods and to use representative clinical data sets.

Machine learning algorithms can relate a multitude of markers—features with a numerical input value—to an outcome value. An example would be to relate fetal heart rate, fetal heart variability and other fetal ECG markers to metabolic compromise as an outcome. Machine learning algorithms need to know how to relate features to an outcome, i.e. the algorithm needs to 'learn' a model. To do so, such an algorithm is trained using a data set for which the outcome is known. An example was

demonstrated in chapter 4, where a machine learning algorithm was trained to relate several EEG-derived features to annotated seizures. The next step after training is to evaluate how well the algorithm can use the model for predicting outcome. This requires the use of data other than that of the training set. If the training set were also to be used for validation, the resulting performance would be inflated due to overfitting. By repeating training and validation using different data each time it is possible to arrive at a relatively unbiased estimate of true performance. Naturally, using an entirely new data set each time training and validation is repeated is often not possible. Luckily, it is also not necessary as various methods exist to randomly divide a data set into training and validation sets.

There is also the issue of the representativeness of the data set used. The data set used for development of the Neoventa ST waveform analysis algorithm seems not to be representative because it lacked negative T/QRS changes in response to hypoxia and acidosis. Machine learning would not have prevented the issue with negative T/QRS changes even though it might have yielded different alarm thresholds for T/QRS changes. The data sets for this dissertation consisted of measurements in an ovine preterm model (chapters 2-4, 6-7) and in human infants (chapter 5). The ovine model we used had the broad advantage of reproducibility of HIE and the ability to do histological investigations. The original experiments with the ovine model were designed to investigate on the one hand the processes involved in HIE and on the other hand potential HIE treatments. The ovine model also had specific advantages and limitations for the purpose of devising algorithm parameters. The main advantage was that measurements were reproducible, that hypoxia-ischemia led to a severe degree of HIE, and that data was measured continuously. These qualities are necessary and sufficient for assessing the usefulness of markers for the first and second stages of brain injury in HIE. The limitation of the ovine model is that results, e.g. threshold values for markers, cannot be directly translated from bench-to-bedside. The processes leading to HIE in clinical practice are more diverse than the hypoxia-ischemia induced by the temporary complete umbilical cord occlusion of our model. Also, while the values of physiological parameters in the ovine fetus are comparable to human fetus or infant in range and in responses to hypoxia and acidosis, they are not the same.

We expect that a major improvement in medical algorithm development in obstetrics and neonatology can be made if a large database of human perinatal physiological signals can be constructed. This database can be used to accurately train and validate algorithms for HIE and other neonatal diseases and disorders. The data to be measured and included in the database should include fetal ECG and fetal blood gas analyses before birth, and at least ECG, EEG (reduced 10/20 system), blood pressure, body temperature, and blood gas analysis after birth. A challenge in developing the database will be the fact that despite the major consequences of neonatal encephalopathy on the global scale, the actual occurrence is relatively low at an estimated 1.5 cases per 1000 live births. Hence a large number of recordings has to be made to capture a reasonable cross-section of clinically occurring HIE. Such a database was unavailable for this thesis. Setting it up will require not only the efforts of a large group of gynaecologists and neonatologists, but also the support of experts in advanced signal analysis and machine learning.

The algorithms developed and described in chapters four and five for calculating marker values can be directly used for further investigations. The algorithm described in chapter four is a novel approach to use temporal information in subsequently measured values of features or markers in a machine learning algorithm. Such an approach is especially useful if the event to be identified has a short temporal duration and cannot be identified based solely on feature values at each separate time point.

The algorithm on burst synchrony investigation as described in chapter five can be directly implemented into EEG monitoring devices, albeit not in devices intended for amplitude-integrated EEG monitoring. The latter devices commonly use only one or two EEG channels, which does not provide the electrode coverage required. It should be noted that reduction in interhemispheric burst synchrony in HIE has, to our knowledge, only been described qualitatively. Our algorithm allows quantitative investigation of burst synchrony as well.